REMARKS

Claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 36, 44-50, 53, 56, 58, 60-62, 64-69, 73, 75, 79 and 83-87, were pending in the application. Of these, claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 53, 56, 68, 69, 73, 75, 79 and 83-87 had been withdrawn from consideration

Claims 36, 44-50, 58, 60-62 and 64-67 were examined and have been rejected.

The following claims are being amended by introduction of limitations from several of the previously pending dependent claims:

- Claim 36: *inter alia*, added limitations from claims 50, 53, 67 (now canceled)
- Claim 49: dependency changed
- Claim 60, 61, 63 and 64: "**an** inflammatory condition" amended to "**the** inflammatory condition".
- Claims 61 and 64: agent being administered is limited to "activated protein C"
- Claim 68: the language "the anti-inflammatory or the anticoagulant agent" is amended to read "activated protein C.".

Cancelations: Active claims 48, 50, 53, 56, 66 and 67 are canceled without prejudice or disclaimer. Also being canceled without prejudice or disclaimer are withdrawn claims directed to oligonucleotides and arrays (69, 73, 75, 83-87).

New claims 88 and 89 are added. New claim 88 limits claim 36 to two of the original three sites of single nucleotide polymorphisms (SNP). Claim 89 is discussed after the discussion of the enablement rejections below.

None of the amendments introduces new matter and their entry is requested.

As a result of the foregoing, claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 36, 44-47, 58, 60-62, 64, 65, 68, 88 and 89 are pending.

Of these, claims 36, 44-47, 58, 60-62, 64, 65, 68, 88 and 89 are under active examination (while claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, and 32-34 remain withdrawn

I. Oath/Declaration

The oath or declaration was found to be defective because Applicants incorrectly sought to claim foreign priority under 35 USC 119**(a)-(d)** to Application 2479968 (Canada, October 8, 2004). However, the foreign application was listed on the oath under the wrong section ((relating to 35 USC 119**(e)**.

A Substitute Oath/Declaration is submitted herewith to remedy this inadvertent error.

II. OBJECTION TO SPECIFICATION

The specification was objected to because of the lack of continuing data n the first paragraph of the specification (if no Application Data Sheet has been filed).

Applicants are submitting and ADS herewith to correct this.

The disclosure was also objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 48.

The above amendment to the specification has remedied this.

III. REJECTIONS UNDER 35 USC § 112, 1ST Paragraph

A. Written Description Rejection

Claims 36, 44-49, and 66-67 were rejected as failing to comply with the written description requirement. Claims 50, 58, 60-62, 64 and 65 were free of this rejection

The Action states that the rejected claims are broadly drawn to a method of treating an inflammatory condition in a subject. The claims comprise selecting a subject having a risk genotype in his protein C sequence and administering to this subject an antiinflammatory agent or an anti-coagulant agent.

The specification (page 34) defines a risk genotype as an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. The claims encompass selecting a subject having any polymorphic variant at one or more polymorphic sites in the protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

The instant invention allegedly encompasses selecting a subject (human or non human) having one or more of an "enormous and wide variety" of allelic variants in the protein C gene. Thus the claims encompass the selection of subjects having many different protein C nucleic acid sequences that are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. The specification is considered not to have taught such a large genus of nucleic acids with the recited associations.

The Office first determined whether a representative number of species was described by their complete structure. The instant specification provides the sequence of the protein C gene (SEQ ID NO:1) and discloses several polymorphic variations of this sequence, specifically the specification teaches that the C allele at position 4732 of SEQ ID NO:1 is correlated with decreased survival and increased multiple organ dysfunction in humans with SIRS. Additional

polymorphic variations that are in LD with position 4732 are described, of which only one, at position 4800 (r^2 value of 0.85), was evaluated within the same patient population as 4732 and found to predict significantly patient outcome.

Next, the Office determined whether a representative number of species were sufficiently described by other relevant identifying characteristics (*i.e.,* other than nucleotide sequence, gene name, and specific polymorphic position) that would serve as specific features and functional attributes distinguishing different members of the claimed genus. Here, the specification allegedly does not provide any characteristics that would allow one to identify any particular polymorphic variants of the disclosed sequence that are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome . The Action cites *In re Shokal,* 113 USPQ 283 (CCPA 1957) in connection with the number of species needed to support a claim to a genus:

According to the Action, one of skill in the art cannot envision the detailed chemical structure of all of the nucleic acids encompassed by the claimed methods based on this specification (regardless of the complexity or simplicity of the method of isolation or use). More is required than a mere statement that such nucleic acids are part of the invention while referencing potential methods for their identification. Rather, the nucleic acids themselves (*i.e.*, sequences) are required. The Action concluded that the limited information in the specification is insufficient to reasonably convey to one skilled in the art that Applicant was in possession of the method as broadly claimed.

B. Applicants' Response

While Applicants do not agree with this ground for rejection, they are limiting claim 36 in several ways that overcome this ground for rejection, although for reasons discussed below, claim 36 is broader than what the Office initially considered to be adequately described. (Limitations related more to the enablement rejection are discussed separately in Section III, D, below.)

(1) The primary SNPs are limited to three positions in SEQ ID NO:1 or SEQ ID NO:2 as imported from claim 50 which was free of this rejection (and is now canceled).

(2) SNPs in LD with the above three position are those appearing in claims 53 and 56.

Thus, the present claims do specifically identify particular polymorphisms.

The Examiner appears to have understood the specification (incorrectly) to indicate that the data for SNP 4800 puts it in LD with the SNP at 4732 (of SEQ ID NO:1) (page 80). Applicants now understand how this happened. To clarify, based on the haplotype map (Figure 1), SNP 4800 is a combination SNP that is in LD with the SNP at 2418 (of SEQ ID NO:1) when

combined with position 2405 or 4919 or 4956 or 6187 or 12109. The amended claims read accordingly. Alternatively, SNP 4800 acts as a combination SNP that is in LD with SNP 4732 (of SEQ ID NO:1) if combined with position 3220 or 9198.

The specification provides data for each of SNPs 4732 of SEQ ID NO:1, 4054 of SEQ ID NO:2 and 2418 of SEQ ID NO: 1 (for example, see Example 2 pages 74-83; Example 1 pages 71-74; Example 3 (combination) pages 84-88; Example 4 (XIGRIS™ treatment) pages 88-112).

As for the issue of representative number of species that support a generic claim, please note that polymorphisms in LD as described in the application (*e.g.*, pages 37-41) are predictive of patient outcome, particularly those having a significantly high degree of LD. However, no such generic language claiming SNPs remains after the present amendments.

In view of the amendments and for the reasons discussed above, and it would be proper to withdraw the rejection under 35 U.S.C. § 112, fist paragraph, for lack of adequate written description.

C. Enablement Rejection

All of the active pending claims (36, 44-50, 58, 60-62, and 64-67) were rejected for lack of enablement.

The Action stated that the specification ***does enable*** claims to a method of treating SIRS in a human subject, by selecting a subject who is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO:1 and administering activated protein C to that subject.

However, allegedly, the application does not reasonably enable claims to a method of treating any inflammatory condition in any subject by selecting a subject having a risk genotype in his protein C sequence and administering any anti-inflammatory agent or an anti-coagulant agent to that subject.

The following points were made in the Office's Wands analysis

(1) Nature of the invention and the breadth of the claims

The claims are broadly drawn as noted above. The specification (at page 34) defines a risk genotype as an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. As such the claims encompass selecting a subject having **any** polymorphic variant at one or more sites in the protein C gene that is associated with decreased likelihood of recovery from an inflammatory condition or increased risk of having a poor outcome. According to the Office, only claims 50, 58, and 62 define

polymorphic variants in the protein C gene that are associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

The claims encompass any type of inflammatory condition. Only claims 48 and 49 recite specific types of inflammatory conditions. The claims encompass any subject (human and non-human).

Only claims 66 and 67 recite specific anti-inflammatory agent or anti coagulant agent

The "nature" of the broader claims requires selection of subjects having many different protein C nucleic acid sequences which are correlated with decreased likelihood of recovery from any inflammatory condition (or an increased risk of having a poor outcome) and administering to such a subject any antiinflammatory / anti-coagulant agent.

(2) Guidance in the Specification and Working Examples

Example 2 teaches an association between the C allele (nucleotide) (in heterozygous or homozygous form) at position 4732 of SEQ ID NO:1 and altered survival and organ dysfunction in critically ill human adults with SIRS, *i.e.*, correlating this SNP with decreased survival and increased multiple organ dysfunction. The specification also discloses other polymorphic variations that are in LD with position 4732. Of these, allegedly only the one at position 4800 (r^2=0.85) was evaluated within the same patient population as 4732 and found to significantly prediction (presumably this refers to statistical significance) patient outcome.

Example 4 discloses whether or not treatment with activated protein C (XIGRIS®) can reduce organ dysfunction in subjects with sepsis who have a risk genotype in protein C characterized by the C allele at position 4732. The 28 day survival rates for patients who had CC/CT in position 4732 of the protein C gene were compared to patients with TT at the same position - with and without XIGRIS® treatment. The results indicated that XIGRIS® treatment increased survival (compared to no treatment) in patients who had the CT and CC genotypes (Fig 7). XIGRIS® treatment had virtually no effect survival >28 days in patients who had T/T at this position.

The Office interpreted these results as enabling a method for treating SIRS in a human subject, which method comprises selecting a subject who s homozygous (C/C) or heterozygous (C/T) at position 4732 of SEQ ID NO:1, and administering activated protein C to the subject.

The present specification allegedly does not provide guidance on how to predictably reach an association between any SNP variant at one or more positions of the protein C DNA sequence and altered survival and organ dysfunction in critically ill adults with SIRS. The specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID

NO:1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction.

As for the disclosed polymorphisms that are in LD with position 4732, only one, at position 4800 (r^2 value of 0.85) was evaluated within the same patient population as 4732 and found to significantly predict patient outcome. However there is no correlation disclosed to exist between the SNP at position 4800 and increased survival when the subject is treated with XIGRIS® (activated protein C).

All of the results in the specification are allegedly limited to patients with SIRS, yet the claims encompass patients with any type of inflammatory condition. The claims encompass human and non human subjects while the disclosure is limited to humans. Although the specification teaches that XIGRIS® treatment increases survival (compared to no treatment) of patients who were CT/CC at position 4732 of protein C DNA, there is no exemplification of success (increased survival) in treating subjects with the foregoing genotypes with any **other** anti-inflammatory / anti-coagulant agent (compared to no treatment).

(3) The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is allegedly even higher. The level of unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Given the large size of the protein C gene (>10 kb), the Action notes that numerous mutations would be expected in this gene. However the specification does not teach a predictable means for

(a) distinguishing between variations that are correlated with altered survival and organ dysfunction in critically ill SIRS patients and naturally occurring variations.

(b) identifying additional variations in the protein C gene that are correlated with altered survival and organ dysfunction in critically ill SIRS patients

The specification allegedly teaches only two protein C gene variants, at positions 4732 and 4800 of SEQ ID NO:1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. The specification teaches several variants that are in LD with the SNP at position 4732. However it is highly unpredictable whether a polymorphism in LD with the SNP at position 4732 of SEQ ID NO:1 will be associated with altered survival and organ dysfunction in critically ill adults with SIRS 95%, 90%, 80%, or 75% "of the time". This unpredictability is allegedly highlighted by **Langdahl** (*J Bone Mineral Res* 2000) which teaches that LD between

alleles is population-dependent, and considerable variation may exist between the frequencies at which alleles are inherited. For example **Langdahl** states that, whereas one group reported that a repeat polymorphism in the IL-1ra gene was in LD with the IL-1β (+3954) SNP, the authors were unable to show linkage between these polymorphisms.

According to the Action, **Wall** (*Nature Reviews Genetics* (2003) *4*:587-97) teaches that LD refers to the fact that particular alleles at nearby sites can co-occur on the same haplotype more often than is expected by chance (page 587, 1st col., 1st para.). **Wall** states that patterns of LD are known to be noisy and unpredictable, because pairs of sites tens of kb apart might be in complete LD, whereas nearby sites from the same region may be in weak LD (pg 587, 2nd col., last para). According to **Wall**, population history, population size, and population structure lead to differences in LD (page 588, 1st col., top), and states that "Measuring LD across a region is not straightforward" (box 1, last para., page 588). According to Wall, it is difficult to compare directly results from different LD studies because of the variation in study design and methods of data analysis (page 591, 2nd col, 1st full para); there are clear differences in LD between Africans and non-Africans (page 593, 1st col). Thus, LD is not predictable. As such both **Langdahl** and **Wall** support the unpredictability of making associations between SNPs that in LD with the SNP at position 4732 of SEQ ID NO:1 as a basis for selecting a subject with SIRS and with altered survival / organ dysfunction.

The Office also notes the unpredictability of extrapolating from humans to other organisms. It is also unpredictable as to whether the results obtained with SIRS can be extrapolated to other inflammatory conditions. The claimed genus of inflammatory conditions is quite large, each condition allegedly having its own pathology and etiology. The specification is allegedly limited to showing an association between the T4732C mutation and altered survival and organ dysfunction in human patients with SIRS. The Action concluded that one cannot extrapolate results from SIRS subjects to any type of inflammatory condition. (See Applicants' comments on this latter point, below.)

Finally, the Action states that it is unpredictable whether results obtained using activated protein C can be extrapolated to treatment with other of anti-inflammatory r anti-coagulant agents. The specification is limited to an association between the C allele at position 4732 of SEQ ID NO:1 and an improved response to therapy with activated protein C. There are no examples in which SIRS patients were treated with other types of anti-inflammatory / anti-coagulant agents. In the absence of evidence to the contrary, it is considered highly unpredictable how SIRS patients with at least one C allele at position 4732 of SEQ ID NO:1 would respond to therapy with other drugs.

(4) Quantity of Experimentation

The specification allegedly teaches two variants in the protein C gene, at positions 4732 and 4800 of SEQ ID NO:1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. Identification of additional protein C gene variants which are associated with such phenotypes in this patient group would require extensive experimentation, and even then, there would be no assurance that any other such predictive variants exist and would be found. And even once such additional variants were found, even more experimentation would be required to determine if individuals harboring them would manifest improved responses to therapy with activated protein C. Such random, trial and error experimentation is considered to be undue; the specification allegedly provides only an invitation to experiment.

Conclusion of Office's Enablement Analysis

Taking into account the foregoing Wands factors, the Office concluded that undue experimentation would be required to make and use the claimed invention to the full claim scope.

D. Applicants' Response

While Applicants disagree with much of the foregoing analysis, to advance prosecution, claim 36 has been limited in several ways that overcome this ground for rejection, although for reasons discussed herein, claim 36 is broader than what the Office now considers to be adequately enabled.

The Office admits that a claim limited to SIRS as the inflammatory condition, a "human" subject, the SNP at polymorphism 4732, and administration of activated protein C as the *anti-inflammatory agent/anti-coagulant agent* are enabled. In partial accordance with this view Applicants have narrowed the following aspects of claim 36:

(i) The subject is now limited to a human.

(ii) The inflammatory condition is now recited as sepsis, septic shock or SIRS.[1]

(iii) The treatment agent is now recited as "activated protein C."[2]

The discussion below focuses on (ii) above and the scope of the SNPs to which the claims have been limited (as discussed above in Section IIIB in connection with Written Description.

1. Inflammatory Conditions

Enabling support for the above scope of inflammatory conditions are found in the specification, where they are defined as follows. "SIRS" is defined at page 52, lines 1-9:

[1] without prejudice to presentation of a broader group of inflammatory conditions in this or a continuation/divisional application

[2] without prejudice to presentation of a broader group of anti-inflammatory/anti-coagulant agents in this or a continuation/divisional application

> A "systemic inflammatory response syndrome" or (SIRS) is defined as including both septic (*i.e.* sepsis or septic shock) and non-septic systemic inflammatory response (*i.e.* post operative). "SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature >38°C or <36°C, B) heart rate >90 beats per minute, C) respiratory rate >20 breaths per minute, and D) white blood cell count >12,000 per mm^3 or <4,000 per mm^3. In the following description, the presence of two, three, or four of the "SIRS" criteria were scored each day over the 28 day observation period.

"Sepsis" is defined at page 52 (lines 10-12) as the presence of at least two "SIRS" criteria and known or suspected source of infection. "Septic shock" was defined as sepsis plus one new organ failure by Brussels criteria plus need for vasopressor medication.

Moreover, an important reference[3] publishing the results of the Consensus Conference Committee of the American College of Chest Physicians/Society of Critical Care Medicine on sepsis and organ failure is submitted herewith (hereinafter "**Bone")**. **Bone,** at page 45, defines "sepsis" as being the same as the definition provided at page 52 of the specification. **Bone** defines "severe sepsis" and "septic shock" in a way that those skilled in the art would consider them encompassed by SIRS. For example:

(1) "severe sepsis" is sepsis with organ dysfunction, hypoperfusion, or hypotension, and

(2) "septic shock" is sepsis induced with hypotension despite adequate fluid resuscitation along with perfusion abnormalities).

It would appear incontrovertible that any patient with sepsis or undergoing septic shock suffers from SIRS as they would, by definition, have at least two of the four SIRS criteria. Furthermore, in the exemplary section of the specification, for example, page 71-113 (specifically, see Tables 8C-8E (pages 81-83), data is presented for sepsis, SIRS and septic shock. In the XIGRIS® treatment in Example 4, the specification provides data for subjects with "severe sepsis" (see page 89 line 8), "sepsis" (see page 109 line 28), and "SIRS" (see page 110 line 4).

The Office has in fact acknowledged[4] that the definition of SIRS includes both septic (*i.e.*, sepsis or septic shock) and non-septic SIRS.

Considering the foregoing, it would be proper to conclude that the present disclosure (coupled with the state of the art) encompasses the language of amended claim 36 with respect to the very limited number of claimed inflammatory conditions. Applicants therefore request withdrawal of this rejection as applied to the scope o the latter term.

According to the Action, claim 50 is not adequately enabled. This claim has been canceled, and its subject matter now incorporated into amended claim 36. Claim 50 focused on

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[3] Roger C. Bone *et al.*, "Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis," The ACCP/SCCM Consensus Conference Committee: Chest (1992) *101*:1644-55, Submitted herewith with form SB08A).

[4] at page 17 of the Action, in the context of the discussion of the § 102 rejection directed to claims 48 and 49.

the risk genotype being present as a SNP at positions 4732 of SEQ ID NO:1, position 4054 of SEQ ID NO:2, and position 2418 of SEQ ID NO:1;or a SNP site or combination of sites in LD with the foregoing 3 positions.

2. SNP Positions

The Office's judgment on this point may in part result from an overly conservative view of the LD claim language relying on **Langdahl** and **Wall**. The broadest claim (36) is **not** being limited to the SNP at position 4732 (which the Action suggests is the only SNP that is adequately enabled) because, as discussed above, the specification also adequately supports the SNPs associated with positions 4054 (SEQ ID NO:2) and 2418 (SEQ ID NO:1).

Discussion of "Linkage Disequilibrium" (LD) and Polymorphism Analysis Using LD and their Predictive Value

With a view to assisting the Examiner and for a more complete administrative record in this case, a more comprehensive discussion follows of LD disequilibrium and the predictability of polymorphisms in LD with a polymorphism for which an association has been made.

In general, the term "linkage" as used in population genetics refers to the **co-inheritance** of two or more non-allelic genes or sequences due to the close proximity of these loci on the same chromosome, which after meiosis remain associated more often than the 50% expected for unlinked genes. However, during meiosis, a physical crossing-over between individual chromatids may result in recombination. Recombination generally occurs between large segments of DNA: contiguous stretches of DNA and genes are likely to be moved together in a recombination (crossing-over) event. Conversely, regions of the DNA that are far apart on a chromosome are more likely to become separated during crossing-over than regions of DNA that are more proximate. Polymorphic molecular markers such as SNPs are often useful in tracking meiotic recombination events, and serve as "positional markers" on chromosomes.

The "pattern" of a set of markers along a single chromosome is referred to as a "haplotype". Accordingly, groups of alleles (*i.e.*, not allelic to one another) on the same short chromosomal segment tend to be transmitted together. Haplotypes on a given chromosomal segment are generally transmitted to progeny together (the haplotype remains intact) unless there has been a recombinational event *within* the haplotype. Absent such a recombination event, for mapping purposes a haplotype can be treated as an allele at a single highly polymorphic locus.

The preferential occurrence of a disease gene in association with specific alleles of linked markers, such as SNPs or other polymorphisms, is called "Linkage Disequilibrium" (LD). This sort of disequilibrium generally implies that most of the "disease chromosomes" carry the same

mutation, and that the markers being tested (serving as disease gene surrogates) are relatively close to the disease gene(s).

For example, in SNP-based association analysis and LD mapping, SNPs can be useful for identifying polymorphisms associated with a pathological condition such as sepsis. Unlike linkage studies, which usually require information from related individuals in affected families, association studies may be conducted within the *general* population. In a SNP association study, the frequency of a given allele (*i.e.* the SNP allele) is determined in numerous subjects having the condition of interest and in an appropriate control group. Significant associations between particular SNPs, or SNP haplotypes, and phenotypic characteristics may then be determined by any of a large number of well-known statistical methods.

Association analysis can either be "direct" or "LD-based." In direct association analysis, potentially causative SNPs may be tested as candidate pathogenic sequence. In LD-based SNP association analysis, SNPs may be chosen at random over a large genomic region or even genome-wide, to be tested for their LD with a pathogenic sequence or pathogenic SNP.

Alternatively, candidate sequences associated with a condition of interest may be targeted for SNP identification and association analysis. Such candidate sequences usually are implicated in the pathogenesis of the condition of interest. For example, in identifying SNPs associated with inflammatory conditions, candidate sequences may be selected from those already implicated in the pathway of this condition/disease. Once identified, SNPs found in, or associated with, such sequences, may then be tested for their statistical association with an individual's prognosis or susceptibility to actually manifesting the condition.

For an LD-based association analysis, high density SNP maps are useful for positioning random SNPs relative to an unknown pathogenic locus. Furthermore, SNPs tend to occur with great frequency and are often spaced uniformly throughout the genome. Accordingly, **SNPs are more likely than other types of polymorphisms** to be found in close proximity to a genetic locus of interest. SNPs are also mutationally more stable than *variable number tandem repeats* (VNTRs).

As noted, in the field of population genetics,[5] LD refers to the *preferential association of a particular allele, for example, a mutant allele associated with a disease, with a specific allele at a nearby locus more frequently than would be expected by chance.* This implies that alleles at separate loci are inherited as a single unit.[6] Accordingly, the alleles at these loci, and the

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[5] Several references are cited here but are *not* being submitted.

[6] Gelehrter, TD and Collins, FS (1990). *Principles of Medical Genetics*. Baltimore: Williams & Wilkens

haplotypes constructed from their various combinations, serve as useful markers of phenotypic variation due to their ability to mark clinically relevant variability at a particular position.[7] This viewpoint is further substantiated by Khoury *et al.*[8] who state, at page 160:

> "[w]henever the marker allele is closely linked to the true susceptibility allele and is in [linkage] disequilibrium with it, one can consider that the marker allele can serve as a **proxy** for the underlying susceptibility allele."

(emphasis added).

As used in the present application, LD is the occurrence in a population of certain combinations of linked alleles in greater proportion than would be expected from the allele frequencies at the loci (*i.e.*, by chance alone). For example, the preferential occurrence of a disease gene in association with specific alleles of linked markers, such as SNPs, or between specific alleles of linked markers, are considered to be in LD. This sort of disequilibrium generally implies that most of the disease chromosomes carry the same mutation and that the markers being tested are relatively close to the disease gene(s). Accordingly, if the genotype of a *first locus* is in LD with a *second locus* (or a *third locus*, *etc.*), ascertaining the allele at only one locus would, by definition, provide the identity of the allele at the other locus.

When evaluating loci for LD, those sites within a given population having a high degree of LD (*i.e.*, an absolute value for D' of ≥ 0.5 or $r^2 \geq 0.5$) are potentially useful for predicting the identity of an allele of interest (*i.e.*, one associated with the disease/condition of interest). A higher degree of LD may be represented by an absolute value for D' ≥ 0.6 or $r^2 \geq 0.6$. Alternatively, a higher degree of LD may be represented by an absolute value for D' of ≥ 0.7 or $r^2 \geq 0.7$ or by an absolute value for D' of ≥ 0.8 or $r^2 \geq 0.8$. Additionally, an even high degree of linkage disequilibrium may be represented by an absolute value for D' ≥ 0.85 or $r^2 \geq 0.85$ or by an absolute value for D' ≥ 0.9 or $r^2 \geq 0.9$. Accordingly, two SNPs that have a high degree of LD may be equally useful in determining the identity of the allele of interest such as a disease allele. Therefore, it may be assumed that knowing the identity of the allele at SNP#1 is representative of the allele identity at SNP#2 that is in LD with SNP#1. Accordingly, determination of the genotype of a single locus can provide the identity of the genotype of any locus that is in LD therewith, and the higher the degree of LD, the more likely it is that two SNPs may be used interchangeably.

LD is useful for genotype-phenotype association studies. For example, if a specific allele at one SNP site (*e.g.*, "A") is the cause of a specified clinical outcome (which we shall call "B")

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[7] Akey, J. *et al.* (2001) "Haplotypes vs. single marker linkage disequilibrium tests: what do we gain?" *European Journal of Human Genetics. 9*:291-300; Zhang, K. *et al.* (2002) "Haplotype block structure and its applications to association studies: power and study designs." *American Journal of Human Genetics. 71*:1386-94

in a genetic association study, then, by mathematical inference, any SNP (*e.g.,* "C") which is in significant LD with the first SNP, will show some degree of association with the clinical outcome. Said differently, if A *is associated with* (symbolized by ~) B (notated as A~B) and C~A, it follows that C~B. Of course, the SNP that will be most closely associated with the specific clinical outcome, B, is the "causal SNP" – the genetic variation that is mechanistically responsible for the clinical outcome. Thus, the degree of association between any SNP, C, and a clinical outcome will depend on LD between A and C.

Until the mechanism underlying the genetic contribution to a specific clinical outcome is fully understood, knowledge of LD helps identify potential candidate "causal SNPs" and also helps identify a range of non-causal SNPs that are nevertheless clinically useful for **prognosis of** (i) a clinical outcome or (ii) a treatment effect. If one SNP within a gene is found to be associated with a specific clinical outcome, then other SNPs in LD with it will also be associated with the outcome and therefore will also be of prognostic value.

Further Amendments to Claim 36

In addition to the other aspects of claim 36 narrowed here by amendment, the present limitation of clam 36 (and its dependent claims as well a the new claims) to specific SNPs place the scope of the claims within that which the Office (i) already accepts as enabled, or (ii) should accept as enabled in view of the present remarks. To reiterate, Applicants contend that data in the application provide direct support for three different SNPs (at 4732, and 2418 in SEQ ID NO:1 and 4054 in SEQ ID NO:2,) and those additional SNPs that are in LD therewith (based on high r^2 values).

Many of the points in **Langdahl** and **Wall** relied upon by the Office relate to the alleged unpredictable nature of sites in LD where the LD is "weak." However, as noted here (and in the specification) the SNPs in LD being claimed here are in "strong LD" (*i.e.*, they have high r^2 values) and therefore have predictive value. The Action at page 12 refers to the following statement in Wall:

> "patterns of LD are known to be noisy and unpredictable as pairs of sites tens of kilo bases apart might be in complete LD, whereas nearby sites from the same region can be in weak LD"

This is in fact entirely consistent with the data presented in the application. For example, in Figure 1, SNPs in the protein C gene are represented by haplotype, wherein one of the lead SNPs at position 4732 is shown to be in LD with the SNP at position 4813 as well as the SNP in position 12228, but is not in LD with more proximate SNPs (such as the SNP at position 6094).

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[8] Khoury *et al.* (1993) *Fundamentals of Genetic Epidemiology.* New York: Oxford University Press

Similarly, the Action's reference at page 12 to *"variation between frequencies at which alleles are inherited"* (based on **Langdahl**) is well-known and well-understood in the art. However, as already stated above, the claimed SNPs in LD have a relatively high r^2 value, so that their predictive value is similarly high. The Office's relied (at page 12) on the inability of **Langdahl** to replicate results from another group that had reported that two polymorphisms were in LD. The Examiner's own comments regarding **Wall** (sentence bridging pages 12 and 13 of the Action) suggests the answer, whereby it is "difficult to compare different LD studies" on the basis that variation in study designs, methods, *etc.* Nevertheless, such a criticism is nothing new to the field and is not really relevant in assessing the patentability of the present claims.

Furthermore, the Action cites **Wall** concerning differences in LD between Africans and non-Africans. The present inventors also tested different ethnic groups, and the specification (at pages 109-112; Example 5) provides data obtained from patients of Asian decent as compared to Example 4, pages 89-109, where the data are not limited by the patients' ethnic origin. Based on general notions discussed in **Langdahl** and in **Wall** that LD analysis may, in some instances, be unpredictable, the Office is using too broad a brush if it is actually espousing the view that that LD analysis is *per se* unpredictable as the basis of its enablement rejection (as regards the SNPs). However, absolute certainty is not a requirement (see below).

Consider the analogy that many drugs do not evoke the same response in all patients even though they are generally effective in the treatment of a specific condition. For example, as demonstrated coincidentally in the present application, activated protein C is a drug that does not appear to have a completely predictable effectiveness in the population as a whole. Nevertheless, activated protein C is an effective treatment entitled to patent protection. It is well established that certainty is not required. The Federal Circuit in *Atlas Powder* v. *E. I. Dupont* (224 USPQ 409, 1984) discussed enablement as it relates to a large group of potential compounds based on a particular formula. The court decided that even if some of the claimed combinations were inoperative, the claims were not necessarily invalid as it is not a function of claims to specifically exclude possible inoperative substances and unless the number of inoperative combinations becomes significant and in effect forces undue experimentation in order to practice the claimed invention; under such circumstances, the claims might be invalid. The use of prophetic examples does not automatically make a disclosure non-enabling. The burden "falls on the party challenging validity to show by clear and convincing evidence that the prophetic examples together with other parts of the specification are not enabling "(emphasis added).

Applicants respectfully submit that the Office as not met this burden. Moreover, Applicants respectfully remind the Office that the enablement requirement does not require proof

of safety and efficacy at levels that might be required for regulatory approval of an agent or treatment. See *Scott v. Finney*, 34 F. 3d 1058, 1063, 32 USPQ 2d 115, 1120 (Fed. Cir. 1994): "Testing for full safety and effectiveness of [an invention] is more properly left to the [FDA]".

In view of the amendments and for the reasons discussed above, and it would be proper to withdraw the rejection under 35 U.S.C. § 112, fist paragraph, for lack of enablement.

Applicants note here that new claim 89 resembles claim 36, is written "independently" of any inflammatory condition because it is directed to a method **of** administering activated protein C to a selected human subject. In that form, the limitation to a narrow set of inflammatory conditions would not be necessary for the claim to meet the written description and enablement requirements of § 112.

IV. PRIOR ART REJECTIONS

The Action notes specifically that the claims rejected below over prior art have also been rejected as not fully described or enabled. The Action states that where the prior art does anticipate or render obvious particular embodiments of the broadly claimed methods, the prior art is not a sufficient basis for compensating for the inadequate written description and enablement of the full scope of the claims.

A. REJECTIONS UNDER 35 USC § 102 (Anticipation)

Claims 36, 44-45, 48, and 49 were rejected under 35 U.S.C. 102(b) as being anticipated by **Yan** *et al.*, (Chest 2001) (hereinafter, **"Yan"**) as *evidenced by* **Reitsma** (*Nucleic Acids Research* 1996).

1. Claim 36

Yan conducted a clinical trial to investigate whether protein C levels predict 30 day mortality rate, shock status, duration of ICU stay, and ventilator dependence in patients with sepsis. Seventy of the patients included in the trial had severe sepsis and failure in one or more organ. A total of 63 out of the 70 patients (90%) had acquired protein C deficiency. **Yan** found that presence and severity of acquired protein C deficiency was associated with poor clinical outcome, including lower survival rate, higher incidence of shock, and fewer ICR free and ventilator free days. **Yan** further teaches that the patients were either treated with ibuprofen or a placebo (abstract). As evidenced by **Reitsma** there are at least 160 different known mutations in the protein C gene that result in protein C deficiency (page 157, col 2). Thus **Yan** teaches selecting 63 subjects that have at least one mutation in their protein C gene that causes protein C deficiency and administering to the subject an anti-inflammatory agent such as ibuprofen.

2. Claim 44

Yan teaches that all patients enrolled in the study had an APACHE score calculated at study entry (page 916).

3. Claim 45

Yan teaches that all patients had to exhibit dysfunction of at least one of the following organ systems: cardiovascular, renal, ARDS/pulmonary, or CNS.

4. Claims 48 and 49

Yan teaches that the sepsis patients with a known or suspected site of serious infection had to meet all of the following criteria: core temperature, ~ 38.3°C or < 35.5°C; heart rate, ~90 beats/min in the absence of β-blocker treatment; and respiratory rate, ~20 breaths/min (or minute ventilation, > 0 L/min if the patient requires mechanical ventilation). Here it is noted that the instant specification defines systemic inflammatory response syndrome as including both septic (i.e. sepsis or septic shock) and non-septic systemic inflammatory response (i.e. post operative). The specification teaches that" SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature >38°C or <36°C, B) heart rate >90 beats per minute, C) respiratory rate >20 breaths per minute, and D) white blood cell count >12,000 per mm3 or <4,000 mm3. Since the patients of Yan meet two or more of the criteria in the ACCP guidelines they are being interpreted as having SIRS.

Applicants' Response

Applicants have introduced the features of claim 50 (free of this rejection) into claim 36, and thereby into all the claims that depend from claim 36. These features distinguish claims 36, 44 and 49 from the cited art. The rejection is moot as to claim 48, which is canceled. Therefore, it would e appropriate to withdraw all the rejections under § 102.

B. REJECTIONS UNDER 35 USC § 103 (Obviousness)

1. First Obviousness Rejection

Claim 46 was rejected as being obvious over **Yan** (*supra*)) as evidenced by **Reitsma** (*supra*) in view of "Grinnell *et al.* (EP 0913156 Pub 1999)[9]

The substance of the **Yan** disclosure relied upon by the Office is set forth above.

[9] Applicants believe that the secondary reference here was listed in error and that Kruse, J.A. *et al.*, *J. Amer. Med Assoc.*, 1988, was intended.

Yan further teaches that all patients enrolled in the study had an APACHE score calculated at study entry (page 916) but does not disclose a method wherein an APACHE II score >25 is indicative of increased risk.

However **Kruse** allegedly fills that gap, disclosing that APACHE II scores can be used to predict mortality and that patients having an APACHE II score >25 are more likely to die than patients having APACHE II scores <25 (Fig. 2). Thus **Kruse** adds the teaching that APACHE II scores >25 are indicative of increased risk of mortality.

Accordingly, it would have been obvious to have modified the method of **Yan** (as evidenced by **Reitsma**) by determining that subjects with an APACHE score >25 are at increased risk of mortality. Motivation allegedly comes from the knowledge that the APACHE II scoring method is highly predictive of outcome.

Applicants' Response

In view of the amendments to claim 36, Applicants contend that the primary reference is inadequate to support a *prima facie* rejection notwithstanding the combination with APACHE II score reference (**Kruse**).

2. Second Obviousness Rejection

Claim 47 is rejected as being obvious over **Yan** as **evidenced by Reitsma** (*supra*) and in view of Wilkinson *et al.* (*Journal of Pediatrics* 1987) (hereinafter **"Wilkinson"**).

Yan's disclosure is discussed above. **Yan** admittedly does not teach a method wherein two or more organ system failures are indicative of increased subject risk. The Office brings the **Wilkinson** reference for its disclosure that mortality rates for two, three, or four or more failed organ systems were 26%, 62%, and 88% respectively (abstract). Thus **Wilkinson** allegedly fills the above gap in **Yan**, making it obvious to have modified the method of **Yan/Reitsma** by determining that subjects with two or more organ failures were at an increased risk of mortality. This relies on the supposedly well known fact that a correlation exists between the number of failed organs and mortality.

Applicants' Response

In view of the amendments to claim 36, Applicants contend that the primary reference is inadequate to support a *prima facie* rejection even when combined with Wilkinson.

3. Third Obviousness Rejection

Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being obvious over **Yan** as evidenced by **Reitsma** (*supra*) and in view of Grinnell *et al.* (EP 0913156 Pub 1999) (hereinafter **"Grinnell"**).

Yan, discussed above, admittedly does not **teach** a method wherein the antiinflammatory agent is activated protein C. The secondary reference, **Grinnell** (citing to its abstract) teaches administering activated protein C to treat patients with sepsis associated with *acquired protein C deficiency*. The Office concluded that it would have been obvious to have modified the method of **Yan** / **Reitsma** by administering activated protein C as suggested by **Grinnell** since activated protein C is allegedly routinely used to treat sepsis. One of skill in the art allegedly would have been motivated to modify **Yan** in this way because **Yan**(at page 921) teaches that activated protein C may reverse the acquired protein C deficiency in patients with sepsis and improve their outcome.

Applicants' Response

First, this rejection is moot as to claim 66 which is canceled. The limitation from claim 67 is now present in amended claim 36. Neither **Yan/Reitsma** nor **Grinnell** suggest the claimed SNPs. Therefore, the primary reference is inadequate to support a *prima facie* rejection even when combined with **Grinnell**. The Examiner is requested to withdraw this ground for rejection.

In summary, with the amendments to the claims, particularly to claim 36, Applicants believe that they have overcome any *prima facie* obviousness rejection of any of the claims.

V. CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks. Applicants believe they have overcome all the pending grounds for rejection. The application is now in condition for allowance which is earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /Shmuel Livnat/
Shmuel Livnat
Registration No. 33,949

SL:mee

Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528

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